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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SYNTHEGO CORPORATION,

Plaintiff/Counter-Defendant,

v.

AGILENT TECHNOLOGIES, INC.,

Defendant/Counter-Claimant.

CASE NO. 5:21-cv-07801-EJD

DEFENDANT/ COUNTER-CLAIMANT AGILENT TECHNOLOGIES, INC.'S NOTICE OF MOTION AND MOTION FOR PRELIMINARY INJUNCTION AGAINST PLAINTIFF/COUNTER-DEFENDANT SYNTHEGO CORPORATION

Date: June 16, 2022
Time: 9:00 a.m.
Courtroom: 4
Judge: Hon. Edward J. Davila

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NOTICE OF MOTION AND MOTION

PLEASE TAKE NOTICE that on June 16, 2022, at 9:00 a.m., in Courtroom 4, 5th Floor, located at 280 South 1st Street, San Jose, CA 95113,[1] Counter-claimant Agilent Technologies, Inc. ("Agilent") will, and hereby does move pursuant to Federal Rule of Civil Procedure 65 and Civil Local Rules 65-2 and 7-2 for a Preliminary Injunction enjoining Counter-Defendant Synthego Corporation ("Synthego") from making, using, offering to sell, or selling within the United States or importing into the United States its CRISPRevolution sgRNA products, including but not limited to its Halo- and Eclipse-powered product lines ("Accused Products").[2]

This Motion is based on this Notice and Motion, the accompanying Memorandum of Points and Authorities, the declarations of William Marshall, Gary Carter, Denise De Mory, and the Proposed Order, all papers on file in this action, such other evidence and argument as may be presented at or before any hearing, and all matters of which the Court may take judicial notice.

MEMORANDUM OF POINTS AND AUTHORITIES

I. ISSUE TO BE DECIDED – CIVIL L.R. 7-4(A)(3)

Whether Agilent is entitled to a preliminary injunction prohibiting Synthego from manufacturing, using, offering for sale, and selling Accused Products that infringe U.S. Patent Nos. 10,900,034 ("the '034 Patent") and 10,337,001 ("the '001 Patent") (the Asserted Patents)[3].

II. INTRODUCTION

Agilent is a worldwide leader in the design and development of products and services in the life sciences, diagnostics, and chemical markets. Agilent has long been recognized for its expertise in synthesizing genetic materials, including deoxyribonucleic acid ("DNA") and ribonucleic acid ("RNA"). In 2012, a new gene editing technology commonly known as CRISPR, which utilizes what is known as guide RNA ("gRNA") to mark the location where DNA editing is

[1] Agilent scheduled this hearing on the first available date provided by the Court but intends to request an earlier hearing date at the Case Management Conference.

[2] A complete list of Accused Products is set forth in the Declaration of William Marshall at paragraph 2.

[3] Attached as Exhibits 1 and 2 to the Declaration of Denise De Mory.

to occur, made big news. Agilent scientists immediately put their RNA synthesis expertise to work to improve CRISPR functionality and outcomes. The inventions in Agilent's Asserted Patents are universally recognized in the industry as improvements to guide RNA for use in the CRISPR system that enhance the ability to edit DNA in human cells. These improvements increase the likelihood that CRISPR can be used to cure human disease and better understand mammalian biological systems.

This case is about the unauthorized copying and use of Agilent's landmark inventions by a young company started by computer engineers who saw an opportunity to jump on the CRISPR bandwagon. De Mory Decl., Ex. 25 at 5. The founder of this company admits that their products are built on others' innovations: "We are not chemists by training or nature, and so we haven't tried to innovate on the chemistry." *Id*. at 6. In fact, this start-up company's business model is built on seeding the market with cheap or free products that practice Agilent's inventions, and in the process, whether the start-up survives or not, irreparably changing the market in a manner that will prevent Agilent from recouping its investment or reaping the rewards of its innovations. That company is Synthego, and it should be enjoined forthwith.

Because Synthego knows that it will not prevail if the merits are addressed now, Synthego initiated this litigation to delay the inevitable, or perhaps, delay it long enough to irreparably change the market. Synthego anticipatorily filed this case when Agilent approached it to take a license. While Synthego (like the rest of the industry) touts the claimed inventions as ***landmark*** innovations, and publicly proclaims that its practice of the claimed inventions is critical to the effectiveness and success of its products, Synthego makes a complete about face in this litigation. What Synthego described as a "landmark" innovation in its customer-facing marketing and educational materials in 2018 and 2019 before the Asserted Patents issued, it now claims in this litigation was "obvious" as of 2014 (or before).

Synthego's anticipatory complaint does not deny infringement because it can't. Instead, Synthego asserts that some sales are immune from damages under Safe Harbor provisions that immunize certain clinical trials conducted for FDA approval from patent damages. But Synthego knew when it anticipatorily filed this case that only a tiny percentage of its sales might fall into

this category, and thus, the safe harbor provisions provide no basis for a declaratory judgment action that could even potentially avoid liability for its infringing actions. Instead, Synthego's true motivation for filing is included in a footnote in which Synthego promised both *inter partes* review petitions ("IPRs") and a motion to stay. Dkt. 1, n.1. Rather than filing this motion immediately, Agilent waited until it had a chance to evaluate the promised IPRs.

Synthego filed these IPRs on January 6, three months after its anticipatory complaint and eight months after Agilent approached Synthego to take a license. Yet the best alleged prior art that Synthego could muster was art that was already before the Patent and Trademark Office ("PTO") during its original examination of the Asserted Patents. The invalidity theories that Synthego advances—that a prophetic example with no testing or other disclosure to show that the prophetic example will work in a newly discovered CRISPR system anticipates or renders the claims obvious—have already been soundly rejected by the PTO during the prosecution of the Asserted Patents. Thus, there is little chance its IPRs will be instituted, much less successful.

Put simply, Agilent's infringement case is strong and Synthego's defenses are weak. Synthego's business model depends on delaying judgment in this case for long enough that it will be impossible for any player in this market to recover from the market changes caused by its aggressive pricing model. Agilent has suffered and will continue to suffer irreparable harm from Synthego's egregious and infringing conduct, and cannot be compensated with monetary damages. The balance of hardships strongly favors Agilent, and a preliminary injunction will serve the public interest. Agilent respectfully requests that this Court enjoin Synthego forthwith.

III. STATEMENT OF FACTS

Agilent advances quality of life with a broad range of high-quality solutions in life sciences, diagnostics and applied chemical markets, which are sold to customers in all 50 states and 110 countries. Gary Carter Decl. ¶2. Agilent technologies help scientists conduct faster, more accurate research to learn more about cancer, diabetes, Alzheimer's, Parkinson's, autism, and other ailments. *Id.* Among other strengths, Agilent has long been recognized for its expertise in synthesizing genetic materials, including DNA and RNA. *Id*.

A. The Asserted Patents improve the CRISPR-Cas System.

CRISPR is a technology that can be used to edit genes. The primary work in developing the CRISPR system was done in 2012 by Dr. Jennifer Doudna, a professor at the University of California Berkeley, and Dr. Emmanuelle Charpentier, who is now the Director of the Max Plank Institute in Berlin. Dr. Doudna and Dr. Charpentier were awarded the Nobel Prize in Chemistry in 2020 for their CRISPR development work in 2012, which resulted in significant industry excitement and follow-on development.

In the native CRISPR system, a CRISPR-associated protein (called a "Cas" protein) is used to cut DNA at a specific location. To do so, the Cas protein must first bind to the DNA at the specific location. This binding is mediated by a molecule called a guide RNA which binds with both the Cas protein and the DNA at the specific location where the DNA has sequence homology with one end of the guide RNA, thereby positioning the Cas protein in the proper location and conformation to perform its cutting function. *See* Marshall Decl., ¶¶43-45, 47. By synthesizing gRNA to mediate these site-specific DNA breaks, CRISPR technology can exploit natural DNA repair mechanisms to edit a gene of interest. A gene can be disrupted or "knocked-out" by inserting or deleting a nucleotide during DNA repair, thereby permitting study of a gene's function. *See id.* ¶¶46-53. CRISPR technology can also be used to "knock-in" a gene after a DNA break. *See id*. Knock-in gene edits can be useful, for example, in studying the effects of specific gene variants, investigating genome regulation, and repairing defective genes. *See id.*

In its early days, scientists using CRISPR technology faced challenges when the technology was used for gene editing in mammalian (including human) cells. *See* De Mory Decl., Ex. 1 at 2:4-18. In order for the CRISPR-Cas system to be biologically active, or functional in cells, the gRNA has to remain intact, or stable, long enough to interact with the Cas protein and allow for the gRNA:Cas complex to target and bind the specific DNA site. *See id.* at 1:60-2:4. When then-existing guide RNA was utilized in the CRISPR system with mammalian cells, however, exonucleases degraded the guide RNA. *See id*. at 63:53-67. Thus, existing CRISPR components failed to produce consistent, reliable gene editing efficiency. Marshall Decl., ¶54.

Starting in 2013, Agilent put its nucleic acid synthesis expertise to work to improve guide

RNAs for use in the CRISPR system. In 2013 and 2014, Agilent worked on developing improved guide RNAs. To solve the stability problem, Agilent scientists attempted various chemical modifications of guide RNAs to attempt to improve their stability and delivery. *See* De Mory Decl., Ex. 3 at 985. Agilent's proprietary TC-RNA synthesis technology allowed Agilent to create a guide RNA with chemical modifications, synthesize sufficiently long RNA sequences, test modifications at various sites on the guide RNA molecule, and to understand whether any modification(s) improved the stability of guide RNA in the CRISPR system while still maintaining guide RNA functionality, i.e., the guide RNA associating with a Cas protein and targeting the gRNA:Cas complex to the target DNA. *See id*., Ex. 1 at 48:4-19; 66:32-134:52.

In 2013 and 2014, Agilent scientists designed, synthesized, and tested hundreds of modifications and combinations, at various sites on the gRNA molecule. *See* De Mory Decl., Ex. 1 at 66:32-134:52. Each modification had to be tested to determine whether a particular modification at a particular site on the guide RNA, or combination of such modifications, improved, diminished, or killed biological activity in the CRISPR system. *See id.* Many modifications that Agilent tested were unsuccessful. *See id.* at 132:67-133:30.

Ultimately, Agilent invented the synthetic chemically modified gRNAs claimed in the Asserted Patents, with specific chemical modifications of nucleotides that provide identifiable advantages over unmodified gRNAs, while continuing to function as gRNA in the CRISPR system. These synthetic chemically-modified gRNA inventions advanced genome editing applications, for example, by improving upon the stability (*e.g.*, De Mory Decl., Ex. 1 at 2:1-8, 31:47-32:43, 35:31-41, 44:38-45:2, 63:53-67), functionality (*e.g.*, *id*. at 63:36-52, 134:40-52), transfectability (*e.g.*, *id*. at 3:60-4:2), and effective delivery of gRNA, including sgRNA, into cells (*e.g.*, *id*. at 34:39-41, 35:31-41, 44:8-12, 62:38-63:32), and minimizing their immunostimulatory response in cells after transfection (*e.g.*, *id*. at 134:29-39).

B. Synthego and the entire industry tout Agilent's innovations as seminal, landmark, and groundbreaking.

Agilent filed its first provisional application for the Asserted Patents in December 2014, and further provisional applications were filed in April and November 2015. *See* De Mory Decl.,

Ex. 1 (cover page). Having already tested hundreds of potential modifications and with the invention firmly in hand, Agilent inventors teamed up with researchers at Stanford University to further demonstrate the efficacy of the inventions in human primary cells.

The Agilent inventors selected several specific chemical modifications, which had already been tested and verified to be inventive at Agilent, for the joint study with Stanford. The tests at Stanford further verified the significance of Agilent's inventions; the Agilent inventions were first made public in a paper published jointly with Stanford researchers in June 2015 in the scientific journal *Nature Biotechnology* entitled "Chemically modified guide RNAs enhance CRISPR-Cas genome editing in human primary cells." De Mory Decl., Ex. 3 ("the Hendel paper"). The Asserted Patents cite to the Hendel paper throughout the specifications; both patents explicitly incorporate the Hendel paper "in its entirety." *Id.*, Ex. 1 at 58:21-24; Ex. 2 at 57:50-51.

The Hendel paper has been cited a remarkable 775 times in other scientific journals since its June 2015 publication. Marshall Decl., ¶65. Agilent's chemically modified guide RNAs advanced CRISPR technology so markedly that publications citing the Hendel paper have called Agilent's work "pioneering," "seminal," and "a major contribution." *Id.*, Ex. 4 at 4; Ex. 5 at 681.

Prior to the issuance of the Asserted Patents to Agilent, Synthego publicly acknowledged that its products include the chemical modifications set forth in what it calls the ***landmark*** Hendel paper. In 2018, Synthego released an educational video explaining why it includes the infringing modifications in its products: "Well several years ago now there was a landmark paper that came out of Matthew Porteus' Lab at Stanford University showing that you could utilize these chemically modified guide RNAs to effectively edit many different types of human primary cells." De Mory Decl., ¶56. Synthego touts the benefits of Agilent's inventions to customers, encouraging the infringement of others. Synthego's website explains that Agilent's inventions that were published and shared with the world in the Hendel paper, "set the bar as the method of choice for CRISPR-Cas9 in primary human immune cells." *Id.*, Ex. 52 at 6.

C. The Asserted Patents were issued over prophetic and untested disclosures like those included in the references Synthego cites in its IPRs.

Despite repeatedly acknowledging the landmark nature of Agilent inventions disclosed in

the Hendel paper, Synthego now claims in litigation and before the PTO that the inventions were obvious in 2014. But the prior art Synthego cites and the obviousness theories in its IPRs have already been rejected by the PTO.

In December 2015, Agilent filed the patent application that led to the issuance of the '034 Patent in January 2021. De Mory Decl., Ex. 1. In February 2018, the PTO rejected 26 of the 29 originally-filed claims as anticipated by U.S. Patent Application Publication 2017/0166893, the original CRISPR patent application filed by Nobel Prize winners Jennifer Doudna, Emmanuelle Charpentier and others ("Doudna"), and the other 3 claims as obvious. De Mory Decl., Ex. 7.

Doudna, like the Pioneer Hi-Bred prior art reference Synthego now cites in its IPRs, contains prophetic mention of how certain modifications might improve stability of guide RNAs in the CRISPR-Cas system with no testing data or disclosure to suggest that the prophetic examples would actually work in the CRISPR system. In particular, the examiner noted that Doudna disclosed synthetic guide RNA for use in the CRISPR-Cas system to target a particular sequence in a DNA molecule. *Id.* at 4-5. Further, the examiner noted that Doudna proposed that modifications to the guide RNA could be made to increase stability, including, for example, "modification in 2'-O-methyl moiety and phosphorothioate" and "at least one modification (i.e., less than 26) at 5' end of guide RNA." *Id*. at 5. These were the same modifications claimed in the rejected (and ultimately issued) claims.

Agilent overcame this rejection. Agilent submitted a declaration from inventor Dan Ryan in which he explained why Doudna did not anticipate the pending claims:

> Doudna discusses nucleic acid modifications, but does not disclose any experimental results or data based on guide RNAs having a modification. Doudna does not indicate if the modifications would increase, decrease, or eliminate gRNA activity.
>
> In my opinion, in order to produce a functional synthetic guide RNA comprising one or more modifications based on the teachings of Doudna, as well as to identify a use for the modified guide RNA, one would have to test the modification(s) in order to know whether guide RNA activity was present. Doudna merely discloses a laundry list of chemical modifications that can theoretically be applied to RNAs. Based on Doudna and the state of the art at the time the present application was filed, it was not possible to predict which modifications would be beneficial to guide RNAs or, at least, would not render the guide RNA non-functional.

Id., Ex. 9 at 2. Agilent further explained the unpredictability of guide RNAs and that Doudna does

not teach how to design a gRNA comprising one or more modifications and having gRNA functionality or how to predict what modifications would be compatible with guide RNA functionality in the CRISPR system. *Id.*, Ex. 8 at 9-12; Ex. 9 at 2-4.

In late November 2018, the PTO withdrew the Doudna-based rejection, but issued a new rejection based on U.S. Patent Application Publication 2014/0242664 by Zhang. *Id.*, Exs. 10, 11. In response, Agilent explained, among other things, that Zhang failed to disclose any examples or experiments with a synthetic gRNA comprising a modification to a phophodiester linkage, to a sugar, or both. *Id.*, Exs. 12-13. Agilent once again emphasized, including via a second declaration from inventor Ryan, the unpredictability of such modifications in the CRISPR system in the absence of test data. *Id.*

In June 2019, the PTO withdrew its rejection based on Zhang but raised certain technical challenges that were ultimately cured. *Id.*, Exs. 14-16. The PTO issued a notice of allowance of claims in August 2020. *Id.*, Ex. 17.

In May 2017, Agilent filed the application that led to issuance of the '001 Patent. Initially, the PTO rejected the claims in view of the same Zhang and Doudna references, as well as a related Zhang patent. *Id.*, Exs. 18, 19. But Agilent overcame those rejections with a response that relied on a declaration from Inventor Ryan; an in-person meeting; a follow-up telephone interview; and a second sworn declaration from Inventor Ryan. *Id.*, Exs. 20-23. The PTO issued a notice of allowance of claims in March 2019. *Id.*, Ex. 24. The '001 Patent issued on July 2, 2019. Ex. 2.

D. Synthego copied Agilent's patented technology.

Exemplary Claim 1 of the '034 Patent recites:

> 1. A synthetic CRISPR guide RNA comprising:
>
> (a) a crRNA segment comprising
>
> (i) a guide sequence capable of hybridizing to a target sequence in a polynucleotide,
>
> (ii) a stem sequence; and
>
> (b) a tracrRNA segment comprising a nucleotide sequence that is partially or completely complementary to the stem sequence, wherein the synthetic guide RNA has gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to the target sequence, and comprises one or more modifications in the guide sequence, wherein the one or more modifications comprises a 2'-O-methyl.

Id., Ex. 1 at 257:35-47. In simpler terms, the claim requires chemically modified synthetic guide RNA that has the gRNA functionality required in the CRISPR system, which is "associating with a Cas protein and targeting the gRNA:Cas protein complex to the target sequence of interest for editing, where the "one or more of the modifications" includes a 2'-O-methyl. Dependent claims add additional specificity as to the particular modifications, as does exemplary claim 1 of the'001 Patent recites.

Exemplary Claim 1 of the '001 Patent recites:

> 1. A synthetic CRISPR guide RNA having at least one 5'-end and at least one 3'-end, the synthetic guide RNA comprising:
>
> (a) one or more modified nucleotides within five nucleotides from said 5'-end, or
>
> (b) one or more modified nucleotides within five nucleotides from said 3'-end, or
>
> (c) both (a) and (b);
>
> wherein said guide RNA comprises one or more RNA molecules, and has gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to a target polynucleotide, wherein the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both.

Id., Ex. 2 at 243:10-24. Thus, claim 1 of the '001 Patent specifies that the claimed chemically modified synthetic guide RNA that has the guide RNA functionality required in the CRISPR system have (a) one or more modified nucleotides within five nucleotides from said 5'-end, or (b) within five nucleotides from said 3'-end, or (c) both, and wherein the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both. *Id.*, Ex. 2 at 243:10-24.

By its own admissions, Synthego conducted none of its own research and development. Synthego simply copied Agilent's inventions and started selling chemically modified guide RNAs as their own "CRISPRevolution" products, while touting the benefits of Agilent's innovations to advertise its own products. Synthego's Head of Synthetic Biology, Kevin Holden, unabashedly announced that "all of our projects involve the use of these chemically modified synthetic single guide RNAs," and explained that Synthego simply copied what was disclosed in the Hendel paper:

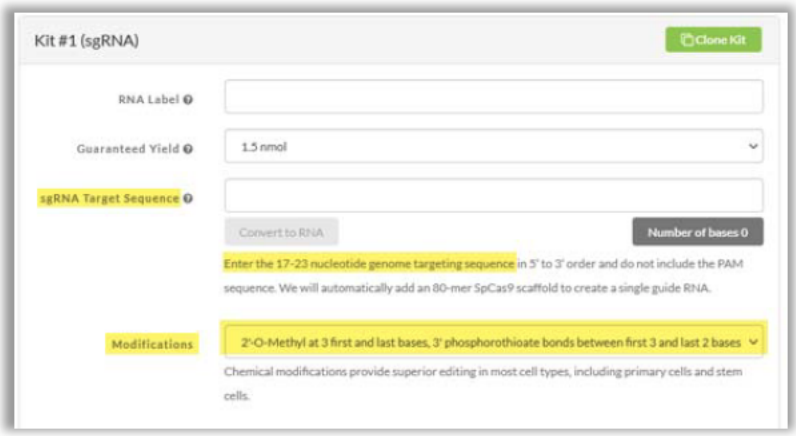
> ***Why do we use these single guide RNAs in a chemically modified format?*** Well, several years ago now there was a landmark paper that came out of Matthew Porteus' lab at Stanford University showing that you could utilize these chemically modified guide RNAs to effectively edit many different types of human primary cells, specifically in this case, primary human T cells and hematopoietic stem cells. And these chemical modifications that exist on the

> guide RNAs they're important for several reasons. ***They actually are these 2'-O-methyl analogs and these sulfur interlinkages on the terminal 3 nucleotides of both ends of the guide RNA molecule.***

De Mory Decl., ¶56.

In its press release announcing "the availability of chemically modified synthetic guide RNA in the CRISPRevolution product family," Synthego explained that its "modified sgRNA are synthesized with 2′-O-methyl analogs and 3′ phosphorothioate internucleotide linkages in the first three nucleotides at both the 5′ and 3′ end of the RNA molecule"—the precise guide RNA modification types and modification locations claimed in the Asserted Patents. *Id.*, Ex. 27 at 1.[4] Synthego advertises that these "[m]odified guides are available as an option to the entire CRISPRevolution synthetic RNA portfolio." *Id.* at 3. Synthego also offers large-scale productions of these chemically modified guide RNAs as "RUO (Research Use Only)," "GMP-like," and "GMP-certified." De Mory Decl., Ex. 28 at 5-6.

In fact, as shown on the CRISPRevolution sgRNA EZ Kit order form on Synthego's website, Synthego's CRISPRevolution sgRNA is a synthetic guide RNA which comprises "modifications" to the "sgRNA target sequence," or guide sequence set forth in the claims of the Asserted Patents, including "2′-O-Methyl at [the] 3 first and last bases, 3′ phosphorothioate bonds between [the] first 3 and last 2 bases."



[4] Synthego sells what are known as single guide RNAs, or sgRNAs. Claims of the Asserted Patent cover both the single guides sold by Synthego and two-piece guide RNAs. Marshall Decl., ¶74.

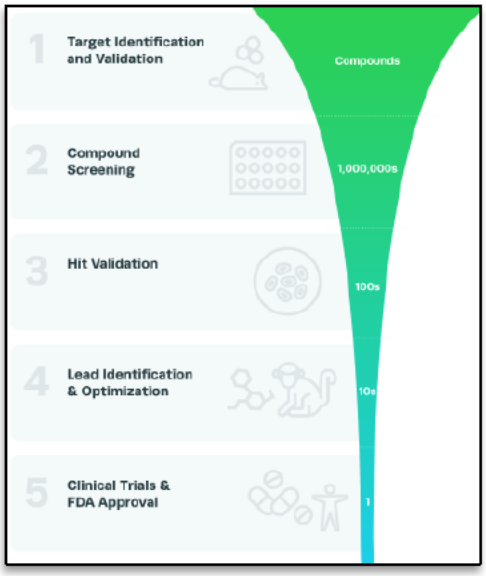
Marshall Decl., ¶79. In fact, Synthego touts the benefits of Agilent's patented modifications right on its order form. Dr. Holden of Synthego confirmed that "all of our projects involve the use of these chemically modified synthetic single guide RNAs . . . They actually are these 2′-O-methyl analogs and these sulfur interlinkages on the terminal 3 nucleotides of both ends of the guide RNA molecule." De Mory Decl., ¶56. Its website also repeatedly touts the modifications: "Our guides are chemically modified to resist degradation and reduce immunogenicity, resulting in high editing efficiencies in difficult-to-edit cell types." *Id.* ¶56.

Synthego expressly recommends that customers utilize chemically modified guide RNAs and offers "free" "modified synthetic single guide RNAs (sgRNAs)," with knowledge that these modified guide RNAs infringe. *Id.* ¶¶115-148.

E. Agilent and Synthego compete in every strata of the guide RNA market, which is a market that is not easily amenable to switching between suppliers.

Agilent sells chemically modified gRNAs covered by the Asserted Patents under the SureGuide and ClinGuide brands. Carter Decl., ¶4. Agilent provides an end-to-end solution for research through therapeutics, selling its commercial embodiments of the Asserted Patents in three distinct markets: (1) small-scale batches of sgRNA products, which allow for sgRNA use in any research application ("research use only" or "RUO"), including the identification of clinically relevant candidates; (2) mid-scale or clinical grade sgRNA products at larger scales, enabling the evaluation of therapeutic modalities; and (3) fully verified "Good Manufacturing Practices" or "GMP" production of large lots of sgRNAs. *Id.*

The RUO market consists of customers using gRNAs for basic scientific research, such as academic institutions. *Id.* at ¶5. The mid-scale market consists of companies or institutions that have advanced past the initial research stage and are exploring the possibility of developing a human therapeutic—i.e., a small molecule, biologics, cell therapies, or gene therapies. *Id.* at ¶6. As depicted in Synthego's explanatory graphic to the right,



this second stage is highly exploratory, well before any therapeutic candidate is selected for clinical testing or regulatory approval. *Id.*

The GMP market generally consists of customers that are using gRNA in connection with clinical trials for human therapeutics, as the U.S. FDA requires that facilities used in connection with such testing and trials must meet the quality control standards set forth in GMP regulations. *Id.* at ¶7. Any gRNA used in connection with clinical trials must be obtained from a GMP-certified facility, as must any gRNAs used in the manufacture of any human therapeutic once approved by the FDA for commercial sale. *Id.*

Agilent and Synthego both have GMP-certified facilities for the manufacture of gRNAs, and both sell their gRNA products to all three of the RUO, mid-scale, and GMP markets. *Id.* at ¶8. These three markets are highly interrelated. Customers who initially purchase their gRNAs from a supplier in one particular market tend to stay with that same supplier for all future purchases of gRNA (in subsequent markets) because switching suppliers can lead to significant delays in getting a therapeutic to market. *Id.* at ¶15. Indeed, Synthego focuses significant marketing efforts on convincing customers that it can support them with their gRNA needs through the entire product development funnel. *Id.*

Indeed, in 2017, Synthego Co-Founder and Chief Executive Officer Paul Dabrowski announced publicly that in starting the company he sought to make guide RNAs "very accessible both from time and cost perspectives," but "we haven't tried to innovate on the chemistry." De Mory Decl., Ex. 25 at 6. Instead, Synthego developed an "RNA factory" to "massively scale" production. *Id.*, Ex. 26 at 6-7. Synthego's "first products included things like chemically modified versions of the single guide RNA." *Id.* Synthego boasts of flooding the market with products using Agilent's innovations at "one-fifth of competitors' prices." *Id.*, Ex. 25 at 6.

In fact, to seed the market with its products, Synthego "started a new RNA access program where we reached out to a lot of key opinion leaders ("KOLs") in the CRISPR space, who we knew were either trying to get these materials or had been buying them at these really crazy costs." *Id.*, Ex. 26 at 7. Synthego targeted and continues to target Agilent's existing and prospective customers, including KOLs, touting the benefits of Agilent's patented chemically modified guide

RNAs, while claiming that Synthego can "make synthetic modified sgRNAs at a smaller scale and cheaper cost." *Id.*, Ex. 29 at 2. Synthego even offers key opinion leaders and other would-be customers "free" "modified synthetic single guide RNAs (sgRNA)." *Id.*, Ex. 30.

F. Synthego rebuffed Agilent's licensing efforts.

The '034 Patent issued in January 2021. On June 24, 2021, Agilent initiated licensing discussions with Synthego. *Id.*, Ex. 35. On July 22, 2021, Agilent representatives participated in a video meeting with Synthego during which Agilent presented a term sheet detailing the basic terms under which Agilent would be willing to license its gRNA-related patents, including the Asserted Patents, to Synthego. *Id.*, Exs. 36, 37.

[redacted] *Id.*

Following the term sheet discussion on July 22, Synthego delayed for several months, offering up repeated excuses for why it needed more time to consider the proposed terms. *Id.*, Ex. 38. Synthego then filed the instant action on October 5, 2021. Dkt. 1.

Synthego's anticipatory complaint does not assert a substantive noninfringement defense but instead weakly claims that its conduct and products are governed by the safe harbor provision in 35 U.S.C. § 271(e)(1), a statute enacted by Congress to protect generic drug developers. *See* Dkt. 1, ¶21. As shown in Section V.A.2, *infra*, Synthego's products and services are not covered by Section 271(e)(1). Synthego also promised IPRs in its complaint. The IPRs have now been filed, and a motion to stay is presumably coming soon. But as shown in section V.A.3, *infra*, Synthego's IPRs are likely to be unsuccessful. There is no reason to delay this action. Indeed, the Court should act expeditiously to protect Agilent's patents and the guide RNA market by preliminarily enjoining Synthego.

IV. LEGAL STANDARD

A motion for preliminary injunction in a patent infringement case is governed by Federal

Circuit law. *See Hybritech Inc. v. Abbott Labs*., 849 F.2d 1446, 1451, n.12 (Fed. Cir. 1988). The Federal Circuit requires the court to consider four factors of "universal applicability" in determining whether to grant a preliminary injunction: (1) likelihood of success on the merits; (2) irreparable harm; (3) the balance of hardships; and (4) the public interest. *See Titan Tire Corp. v. Case New Holland, Inc*., 566 F.3d 1372, 1375–76 (Fed. Cir. 2009). The court "must weigh and measure each factor against the other factors and against the form and magnitude of the relief requested." *Hybritech*, 849 F.2d at 1451.

V. ARGUMENT

A. Agilent is likely to succeed on the merits.

"With regard to the first factor—establishing a likelihood of success on the merits—the patentee . . . must show that it will likely prove infringement, and that it will likely withstand challenges, if any, to the validity of the patent. *Titan Tire Corp. v. Case New Holland, Inc*., 566 F.3d 1372, 1376 (Fed. Cir. 2009). Agilent's infringement case is strong, and Synthego is unlikely to succeed in challenging the validity or enforceability of the '034 and '001 Patents.

1. Synthego's accused CRISPRevolution products and processes infringe the '034 and '001 Patents.

Synthego alleged no facts in its complaint supporting noninfringement because there are none. The evidence indisputably shows that the Accused Products infringe the Asserted Patents. Marshall Decl. ¶¶71-148.

a. Synthego's accused CRISPRevolution products infringe at least claim 1 of the '034 Patent.

The Accused Products infringe at least claim 1 of the '034 Patent. The Accused Products are "synthetic CRISPR guide RNA" as required by the preamble because CRISPRevolution sgRNA is "a chimera of CRISPR RNA (crRNA) and tracer RNA (tracrRNA)," as shown in Synthego's product literature. Marshall Decl., ¶74.

Synthego's CRISPRevolution sgRNA comprises "(a) a crRNA segment comprising (i) a guide sequence capable of hybridizing to a target sequence in a polynucleotide" because CRISPRevolution sgRNA comprises a "CRISPR RNA (crRNA)" segment which includes a

"genomic target specific 17-23 nt [nucleotide] sequence." *Id.* at ¶75. Synthego advertises that the accused products are capable of hybridizing to a target sequence in the CRISPR-Cas system and therefore, the Accused Products meet element 1(a)(i).

Synthego's CRISPRevolution sgRNA comprises a crRNA segment with a stem sequence and a tracrRNA segment with a nucleotide sequence that is partially or completely complementary to the stem sequence because CRISPRevolution sgRNA includes "an 80 nt scaffold that consists of the tracrRNA … and a proprietary linker region connecting the tracrRNA to the crRNA." *Id.* at ¶76. This 80 nucleotide scaffold includes the binding site for the Cas9 protein, which includes a fusion of a tracrRNA segment and a crRNA segment, which are partially or completely complementary and are joined by a "linker region" and therefore meets the stem sequence and tracrRNA segment requirements in elements 1(a)(ii) and 1(b). *Id.*

As advertised, Synthego's CRISPRevolution sgRNA is "compatible with Streptococcus pyogenes Cas9," and when associated with Cas9—as a ribonucleoprotein, for example –these "chemically modified synthetic sgRNAs from Synthego result in consistently high indel frequencies that enable robust editing." Marshall Decl., ¶77. Synthego's CRISPRevolution sgRNA "has gRNA functionality comprising . . . targeting the gRNA:Cas protein complex to the target sequence," as recited in claim 1. CRISPRevolution sgRNA's "genomic target specific sequence" targets the gRNA:Cas protein complex to the corresponding target sequence. *Id.* at ¶78. And, as described above, Synthego advertises that its sgRNAs "result in consistently high indel frequencies that enable robust editing." *Id.* at ¶77.

As shown above in the CRISPRevolution sgRNA EZ Kit order form on Synthego's website, Synthego's CRISPRevolution sgRNA is a synthetic guide RNA which comprises "modifications" to the "sgRNA target sequence," or guide sequence, including "2′-O-Methyl at [the] 3 first and last bases, 3′ phosphorothioate bonds between [the] first 3 and last 2 bases," thereby meeting the final element of claim 1. *Id.* at ¶79.

b. Synthego's accused CRISPRevolution products infringe at least claim 1 of the '001 Patent.

Synthego's CRISPRevolution products also infringe at least claim 1 of the '001 Patent.

The Accused Products are synthetic CRISPR guide RNA with at "at least one 5′-end and at least one 3′-end," and therefore meet the preamble of the claim. Marshall Decl., ¶92.

The Accused Products satisfy elements 1(a), 1(b), and 1(c) because the CRISPRevolution sgRNA has "modifications" including "2′-O-methyl analogs and 3′ phosphorothioate internucleotide linkages at the first three 5′ and 3′ terminal residues" as shown above. *Id.* at ¶93. Synthego's CRISPRevolution sgRNA also "comprises one or more RNA molecules" as recited in claim 1 because it contains the target sequence, or guide sequence, which is added to an "80-mer SpCas9 scaffold" sequence "to create a single guide RNA." *Id.* at ¶94.

Synthego's CRISPRevolution sgRNA also meets the limitation in '001 claim 1 that it "has gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to a target polynucleotide," for the same reasons discussed above with respect to the similar limitation in '034 Patent claim 1. *Id.* at ¶95. Synthego's CRISPRevolution sgRNA has one or more modified nucleotides that has a modification to a phosphodiester linkage, a sugar, or both because, as shown for claim 1 (preamble) above, the first three 5′ and 3′ terminal RNA residues have a modification to a sugar, that is, a 2′-O-methyl, and a modification to a phosphodiester linkage: specifically, a 3′-phosphorothioate internucleotide linkage, and therefore meet the final element of the claim. *Id.* at ¶96.

c. Synthego's accused products infringe other claims of the '001 and '034 Patents.

The Accused Products also infringe at least claims 2-5, 8, and 16 of the '034 Patent and claims 2-3, 6, 9, 21-22, 25, and 27-30 of the '001 Patent. Marshall Decl., ¶¶81-91, 98-145. Synthego also indirectly infringes at least Claim 2 of the '034 Patent and Claims 21-22, 25, and 27-29 of the '001 Patent. *Id.*, ¶¶109-148.

2. The Section 271(e)(1) safe harbor provision does not apply to Synthego's Accused Products.

Synthego's anticipatory declaratory judgment action alleges only that its sales are protected by Section 271(e)(1) of the Patent Act. But as set forth below, Synthego knew before it filed that few, if any, of its sales could even be potentially protected by this statute.

Section 271(e)(1) deems an act that would otherwise constitute patent infringement to be "not [] an act of infringement" if the act is "solely for uses reasonably related" to federal approval. Specifically, Section 271(e)(1) provides:

> *It shall not be an act of infringement to* ***make, use, offer to sell, or sell*** *within the United States or* ***import*** *into the United States a patented invention . . .* ***solely for uses reasonably related to the development and submission of information*** *under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.*

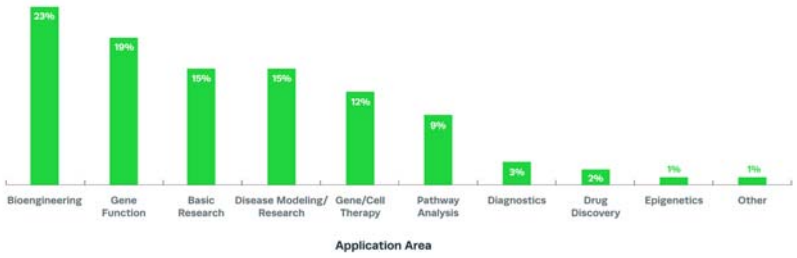
35 U.S.C. § 271(e)(1) (emphases added). "The purpose of section[] 271(e)(1)," as explained by Congress, was "to establish that experimentation with a patented drug product, when the purpose is to prepare for commercial activity which will begin after a valid patent expires, is not a patent infringement." H.R.Rep. No. 98-857, pt. 1, at 45, 1984 U.S.C.C.A.N. at 2678. With the enactment of Section 271(e)(1), "'Congress has said to the public: You may commit acts of infringement and be protected only so long as *those* acts are solely for uses reasonably related to gaining FDA approval to market your product.'" *Safety Syringes, Inc. v. Plastef Investissements*, No. 2:07-cv-2307-FMC, 2008 WL 11337730, at *3 (C.D. Cal. Dec. 11, 2008) (emphasis in original) (quoting *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1277 (N.D. Cal. 1991)).

The statute exempts only acts of infringement that are "solely for uses reasonably related to the development and submission of information" for regulatory approval. All other research, all other acts *before* the clinical trial process, and all other acts *after* the clinical trial process—such as the ultimate sale of an approved drug—are not covered by the safe harbor provision.

Synthego does not allege that its products are used "solely for uses reasonably related to the development and submission of information." Instead, Synthego alleges that its products are "are utilized by thousands of commercial and academic researchers" (Dkt. 1, ¶5), but neither research nor the commercial products that result fall within the safe harbor provision. *See Teva Pharms. USA, Inc. v. Sandoz Inc.*, No. 09-cv-10112(KBF), 2013 WL 3732867, at *7-9 (S.D.N.Y. July 16, 2013) ("When one is not using a patent 'solely' to develop and submit information, one does not fall within the safe harbor."); s*ee also Allelle Biotech. & Pharm., Inc. v. Pfizer, Inc.*, No. 20-cv-01958, 2021 WL 1749903 (S.D. Cal. May 4, 2021); *PSN Illinois, Inc. v. Abbot Labs., Inc.*, No. 9-C-5879, 2011 WL 4442825 (N.D. Ill. Sept. 20, 2011).

Even if a party can show that *some acts* of infringement are "solely for uses reasonably related to the development and submission of information," section 271(e)(1) only protects acts that meet this strict statutory requirement. As a result, this provision does not apply to any of Synthego's RUO sales, which are not "solely for uses reasonably related" to regulatory submission, or any post-approval gRNA sales of any type – RUO, GMP-like or GMP. For example, research use of Synthego's chemically modified gRNA to explore tissue-specific gene expression mechanisms in mice is not covered by the safe harbor. *See Teva*, 2013 WL 3732867, at *7-9. And even for Synthego's drug discovery customers, the statute offers no protection for any post-approval infringing use, i.e., use after regulatory approval. De Mory Decl., Ex. 39.

Synthego only alleges that its customers' use of one product in this list of products—its CRISPR GMP sgRNA product—potentially fall within the safe harbor exemption: "Synthego's customers are using or plan to use Synthego's GMP-grade sgRNAs in upcoming preclinical and clinical trials." Dkt.1 at 2:13-14. And, more importantly, Synthego tracks how customers use its products and knows that, at best, only a very small percentage of its sales may actually lead to clinical trials. As the following bar graph from the Synthego website demonstrates, only 2 percent of Synthego's sales of Accused Products are used in the area of drugs discovery, which would likely be where GMP-grade products ultimately would be used and where clinical trial would likely occur. Another 13 percent are used for what Synthego labels as "gene/cell therapy," which may also ultimately result in clinical trials.



De Mory Decl., Ex. 54. Thus, Synthego's safe harbor defense, at most, may shield some portion of this 15 percent of its sales, and does not shield the vast majority of Synthego's infringing activities. *See Amgen Inc. v. Hospira, Inc.*, 944 F.3d 1327, 1338-39 (Fed. Cir. 2019) (affirming jury verdict where products were found to be not covered by safe harbor as not reasonably

related to regulatory approval); *Isis Pharms., Inc. v. Santaris Pharma A/S Corp.*, 2014 WL 794811, at *4 (S.D. Cal. Feb. 27, 2014). At a minimum, all of Synthego's other sales are infringing and should enjoined.

3. Synthego is unlikely to prove invalidity or succeed with its IPRs.

Synthego has had since at least June of 2021 (and discovery will likely reveal that it became aware of Agilent's Asserted Patents even earlier) to muster up the best art it could find to try to invalidate the Asserted Patents. After indicating that an IPR filing was imminent early last October, Synthego finally filed its IPRs on January 6. The IPRs rely on the same alleged prior art references cited in Synthego's Reply to Agilent's counterclaims. Neither the IPRs nor the Reply are likely to succeed.

The primary reference cited in Synthego's IPRs is Pioneer Hi-Bred—a reference that was before the PTO during prosecution of the Asserted Patents. De Mory Decl., Ex. 49 at 13; Ex. 50 at 13-14; Ex. 1 at page 2; Ex. 2 at page 2. The arguments that Synthego makes about Pioneer Hi-Bred are cumulative of the arguments that Agilent already overcame during prosecution regarding Doudna and Zhang and will fail on the same basis.[5] Thus, it is highly unlikely that the IPR will even be instituted. *See* 35 U.S.C. § 325(d) ("In determining whether to institute or order a proceeding . . . the Director may . . . reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office."). Indeed, the absence of any testing data in Doudna or Zhang was key to Agilent's ability to overcome those references during prosecution. The same arguments will apply to Pioneer Hi-Bred.

The other four prior art references cited in Synthego's Reply are cumulative of the art that Agilent disclosed to the PTO during prosecution, and do not even relate to CRISPR or gRNA. In addition, Synthego admits that the Hendel paper, which is incorporated by reference into the

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[5] There is little question that Synthego is aware of the deficiencies in its IPRs. Its discussion of the prosecution history in the IPRs omits mention of the Doudna rejections, or the manner in which Agilent overcame them – opting instead to characterize only a portion of the argument Agilent made to overcome Zhang. De Mory Decl., Ex. 49 at 10-11; Ex. 50 at 11-12.

specifications of the Asserted Patents, discloses chemical modifications of RNA "selected from known modifications with reported stabilizing benefits." Dkt. 24 at 14:11-12. Thus, the PTO knew that at the time of Agilent's invention there were already known modifications to RNA, and the PTO nevertheless issued the Asserted Patents.

4. Synthego is unlikely to prove inequitable conduct.

As discussed in Agilent's pending Motion to Dismiss (Dkt. 27), Synthego's inequitable conduct claim is doomed to fail because the two references that Synthego alleges to have been improperly withheld from the PTO were in fact disclosed. *See* Dkt. 27, 1:20-4:1. But even if the Court does not dismiss Synthego's inequitable conduct claim at the pleading stage, the chances of Synthego succeeding are low. In *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011), the Federal Circuit significantly raised the bar for proving inequitable conduct. After *Therasense*, a party alleging inequitable conduct must prove both: (1) a material misrepresentation or omission to the PTO, and (2) a specific intent to deceive the USPTO. *Id.* at 1290. Both elements must be proven by clear and convincing evidence. *Id*. at 1287.

Synthego is unlikely to meet its burden of proof on both elements, and particularly with respect to specific intent to deceive which "must be the single most reasonable inference able to be drawn from the evidence." *Therasense*, 649 F.3d at 1290 (quotations omitted). And "where there are multiple reasonable inferences that may be drawn, intent to deceive cannot be found." *Id.* at 1290-91. The minimal allegations made by Synthego to date on inequitable conduct provide little indication that it will be able to muster the necessary evidence during discovery to meet this high threshold for proving intent to deceive. *See* Dkt. 24, 16:1-11.

B. Agilent will suffer irreparable harm absent a preliminary injunction.

To prove irreparable harm, a patentee must establish that (1) absent an injunction, it will suffer irreparable harm, and (2) a sufficiently strong causal nexus connects the alleged harm to the alleged infringement. *Apple Inc. v. Samsung Elecs. Co*., 695 F.3d 1370, 1374 (Fed. Cir. 2012). Both of these requirements are easily met here.

1. There is a likelihood of irreparable harm given the dynamics of the CRISPR/sgRNA market.

Synthego's accused gRNA products directly compete with Agilent's gRNA products in all three markets—the RUO, mid-scale, and GMP markets. Carter Decl., ¶9. Every sale of a gRNA product made by Synthego is therefore a lost sale to Agilent. "Where two companies are in competition against one another, the patentee suffers the harm—often irreparable—of being forced to compete against products that incorporate and infringe its own patented inventions." *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013).

Further heightening the risk of irreparable harm is the fact that the market for gRNA products is currently in an explosive stage of growth. Carter Decl., ¶10. Based on market research, Agilent estimates that demand for gRNA products will increase at an annual rate of 18.1% through 2024. *Id*. With such market conditions, Agilent's loss of market share may not be recoverable in the future. As the Federal Circuit has explained, "[d]uring the growth stage of a product, it is particularly crucial to be able to distinguish oneself from competitors. This includes building the brand, expanding the customer base, and establishing one's reputation and leadership in the market." *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 931 (Fed. Cir. 2012).

2. Monetary damages are insufficient to compensate Agilent for the harm caused by Synthego's infringement.

Absent an injunction, Agilent is likely to suffer irreparable harm that cannot be compensated by monetary damages, including price erosion. Synthego's strategy in the marketplace has been to compete primarily on price, telling potential customers that it can provide its gRNAs at lower prices than any other company, and in some cases even giving away its gRNAs for free. Carter Decl., ¶15. Synthego can sell its gRNAs at lower prices because, as Synthego's CEO admits, it did not have to invest any time or money "to innovate on the chemistry." Instead, Synthego simply copied Agilent's inventions and is now using them to drive down prices. This price undercutting strategy significantly impacts Agilent's ability to reap the rewards of its investment in research and development of its gRNA inventions and the costs of bringing them to market. *See Celsis*, 664 F.3d at 930 ("Price erosion, loss of goodwill, damage to reputation, and loss of business opportunities are all valid grounds for finding irreparable harm.").

Synthego has also irreparably harmed Agilent by persuading key opinion leaders ("KOLs") who previously collaborated with Agilent to effectively switch sides to Synthego's camp. Carter Decl., ¶11. These KOLs previously promoted Agilent's chemically modified gRNAs, but they now appear at conferences and other public events promoting Synthego's competing gRNA products. *Id.* at ¶12. KOLs can greatly influence customers in the marketplace, especially at a time when the market is expanding and it is critical for a company to develop its reputation, brand, and customer relationships. *Id.* at ¶13. KOLs are often associated with prestigious universities or research centers. Becoming a supplier of gRNAs to these KOLs is important for a gRNA manufacturer's reputation. *Id*. If Synthego is allowed to continue providing its infringing gRNAs to KOLs and convincing KOLs to promote its gRNA products instead of Agilent's, Agilent will continue to suffer harm to its reputation. *Id.*; *see also Celsis*, 664 F.3d at 930.

Agilent is also likely to suffer lost business opportunities that cannot be recovered absent an injunction. Customers typically show significant loyalty to their initial gRNA supplier and are reluctant to switch. Carter Decl., ¶14. This is particularly true for companies developing human therapeutics because changing suppliers in the middle of a project can complicate testing results and data, leading to costly delays in getting a therapeutic to market. *Id*. Consequently, once Synthego supplies its infringing gRNAs to any particular customer, it will be extremely difficult for Agilent to convince that customer to purchase from Agilent. *Id*. This loss of potential customers cannot be compensated by monetary damages. *See Celsis*, 664 F.3d at 930.

The potential inability of Synthego to pay damages at the conclusion of this case also weighs in favor of a preliminary injunction. *See Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1155 (Fed. Cir. 2011). Synthego is a private startup company with a questionable revenue stream. While its strategy of selling its gRNAs at lower prices than other companies and giving away its gRNAs for free has helped Synthego gain market share, it is a costly one; Synthego has likely achieved little to no positive net revenue to date. Carter Decl., ¶15. Synthego's strategy of undercutting competitors on price creates a risk that Synthego will not have the means to pay for the damages resulting from its own tactics.

Agilent's offer to license its patents to Synthego and other parties does not negate the

irreparable harm that it will suffer absent an injunction. *See ActiveVideo Networks, Inc. v. Verizon Comms., Inc.*, 694 F.3d 1312, 1340 (Fed. Cir. 2012). Whenever Agilent has offered a license to other gRNA vendors such as Synthego, the terms have included significant restrictions on the scope of the license. Importantly, [redacted], a critical market for Agilent. Carter Decl., ¶9. This restriction is necessary because allowing licensees the unlimited right to practice the patents would erode Agilent's gRNA business in a way that could not be compensated by the mere payment of royalties. *Id.* at ¶14.

On this point, *ePlus, Inc. v. Lawson Software, Inc.*, 2011 WL 2119410 (E.D. Va. May 23, 2011), is instructive. In that case, the court found irreparable harm despite the existence of five pre-existing licenses granted by the patentee that "contained various restrictive limitations as well as the rights to use the patents." *See id.* at *14. The court reasoned that "if no injunction issues, ePlus will be forced to license its patents to Lawson without any of the restrictions and protections that it has negotiated in the other licenses. Those restrictions, of course, can often be as important as the monetary payment for the license." *Id.* at *15. Similarly, absent an injunction, any damages awarded to Agilent at the end of this case would be insufficient to compensate it for the field of use restrictions it could have obtained through its licensing program. *See also Halo Elecs., Inc. v. Pulse Elecs., Inc.*, No. 2:07-cv-331, 2013 WL 3043668, at *5-6 (D. Nev. June 17, 2013).

Finally, Agilent did not unreasonably delay in seeking a preliminary injunction. Agilent waited until the '034 Patent issued in early 2021 and then attempted to engage in licensing negotiations with Synthego before pursuing injunctive relief. *See Heat Factory USA, Inc. v. Schawbel Techs., LLC*, 2019 WL 1779579, at *7 (S.D. Cal. Apr. 23, 2019) (nearly one-year period spent attempting to negotiate a non-judicial resolution did not constitute delay). And the present motion for injunctive relief comes just three months after Synthego's initiation of this lawsuit, when it threatened to file the IPRs that it has now lodged. Agilent reasonably waited to see if Synthego would come forward with some new art that could possibly explain its litigation-motivated switch from acknowledging the inventions as landmark to claiming they are invalid.

But there was none. In any event, delay "is but one factor to be considered by a district court in its analysis of irreparable harm." *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1457 (Fed. Cir. 1988). Thus, even if the Court finds that Agilent should have acted sooner, any delay is outweighed by the multiple forms of irreparable harm discussed above.

3. There is a causal nexus between Synthego's infringement and the irreparable harm to Agilent.

The causal nexus test requires a showing of "some connection between the patented feature and demand for [the accused infringer's] products." *Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1364 (Fed. Cir. 2013). This connection can be shown with evidence "that a patented feature is one of several features that cause consumers to make their purchasing decisions" or "that the inclusion of a patented feature makes a product significantly more desirable." *Id.*

Here, there is a strong causal nexus. The core claimed invention—chemically modified gRNAs with CRISPR-Cas system functionality—is the very product that Synthego is selling. Put simply, there is no other feature of Synthego's accused gRNAs that make them desirable to customers other than the chemical modification covered in the Asserted Patents. Indeed, Synthego repeatedly advises its customers to order its chemically modified gRNAs as opposed to non-chemically modified gRNAs because chemically modified gRNAs provide substantial advantages, including "[i]ncreased stability and protection from exonucleases," "[o]verall improved editing efficiency," "[r]educed innate immune response," and "[r]educed off-targets compared to plasmid or viral delivery." De Mory Decl., Ex. 6; *see also id.*, Ex. 40 ("Chemical modifications provide superior editing in most cell types, including primary cells and stem cells."); *id.*, Ex. 27 ("modified guide RNAs provide protection against intracellular immune responses . . . [and] improves *in vivo* stability"). The benefits of the infringing chemically modified gRNAs are therefore an important (if not the most important) factor in the success of Synthego's products.

C. The balance of hardships weighs in favor of a preliminary injunction.

Absent an injunction, Agilent is likely to suffer irreparable harm. This harm outweighs any harm to Synthego, particularly when Synthego knowingly took a calculated risk to infringe the Asserted Patents. *See Windsurfing Int'I, Inc. v. AMF, Inc.*, 782 F.2d 995, 1003 n.12 (Fed. Cir.

1986) ("One who elects to build a business on a product found to infringe cannot be heard to complain if an injunction against a continuing infringement destroys the business so elected.").

Synthego was well aware of the Asserted Patents through its communications with Agilent, but it took no action to avoid infringement. In addition, Synthego refused to engage in good faith negotiations with Agilent regarding potential licensing of the patents, and instead created the present dispute by filing a declaratory action in this Court. Synthego therefore should not be heard to complain of the harm it may suffer from a preliminary injunction in litigation that it started.

D. The public interest weighs in favor of a preliminary injunction.

The public interest favors a preliminary injunction in this case because protecting Agilent's patent rights promotes innovation in the field of biotechnology. *Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1348 (Fed. Cir. 2006) ("[A]bsent any other relevant concerns...the public is best served by enforcing patents that are likely valid and infringed."). In addition, the public will not be harmed if Synthego is temporarily enjoined from selling the accused products during the pendency of this litigation, as the public can still obtain sgRNA products from Agilent. *See* Carter Decl., ¶8; *Celsis In Vitro*, 664 F.3d at 931-32 (public interest favored injunction because "both LTC and Celsis sell the same products and are in direct competition. In other words, the public can obtain the products from Celsis.").

VI. CONCLUSION

For the foregoing reasons, Agilent respectfully requests that the Court enter an order preliminarily enjoining Synthego from manufacturing, marketing, selling or using any and all Accused Products.

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Respectfully submitted,

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